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(54) Title: MICROSPHERE-IN-OIL EMULSION

(57) Abstract

The present invention provides a novel method for masking the bitter or unpleasant taste of an orally active compound and a method of improving the bioavailability of an active ingredient which has a high hepatic first-pass effect by administering the compound or active ingredient in a microsphere-in-oil-in-water emulsion and compositions suitable for practicing said method.

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MICROSPHERE-IN-OIL EMULSION

FIELD OF INVENTION

This invention relates to a new use for a microsphere-in-oil emulsion, said new use being a method of masking the taste of bitter or unpleasant tasting drugs by formulating said drug in a microsphere-in-oil emulsion for administration to a patient and to compositions useful in practicing said new use.

BACKGROUND OF INVENTION AND PRIOR ART STATEMENT

Microsphere-in-oil emulsions are known in the art and are used for parenteral administration of drugs and more particularly anti-cancer drugs. M. Hashida, et al., International J. Pharmaceutics 2, 245-256 (1979) describes a microsphere-in-oil emulsion which was formed by replacing the inner water droplets of a water-in-oil emulsion with gelled gelatin microspheres. The gelled gelatin microspheres contain bleomycin, and the microsphere-in-oil emulsion was evaluated as an injectable drug delivery system in carcinoma-bearing rabbits. The oil employed in this formulation was a medium chain triglyceride or sesame oil. See also T. Yoshioka, et al., Chem. Pharm. Bull. 30(4), 1408-1415 (1982) wherein a microsphere-in-oil emulsion containing bleomycin is compared to a sphere-in-oil emulsion. A similar microsphere-in-oil emulsion containing 5-fluorouracil was employed in a study to evaluate the stability and drug release characteristics of the emulsion by M. Hasida, et al., Chem. Pharm. Bull. 28(4), 1009-1015 (1980). The

emulsions of this study were found to have good injectability characteristics.

U.S. Patent Number 4,384,975 describes microcapsules formed by the removal of solvent from an oil-in-water emulsion. The active ingredient is dispersed in a polymer dissolved in an organic solvent in which the active ingredient is not soluble, and the organic dispersion is mixed with an aqueous solution containing an emulsifier. The organic solvent is removed by evaporation leaving microcapsules suitable for encapsulation. These microcapsules differ considerably from the microsphere-in-oil emulsion of the present invention in that the drug is dispersed in a polymer, organic solvents are used in formulation, and the solvent is removed. U.S> Patent Number 4,479,911 describes similar microcapsules. U.S. Patent Number 4,652,441 describes microcapsules wherein the active ingredient may be dispersed in gelatin, however, formation of the microcapsules also involves a solvent removal system to provide discrete particles which can be administered as fine granulets, formulated for injection, tableted or formulated as suppository.

The present invention provides a novel use for microsphere-in-oil emulsions, said use being to mask the unpleasant taste of drugs to be administered orally by placing the drug in a microsphere-in-oil formulation. The present invention also is useful in improving the bioavailability of compounds.

SUMMARY OF INVENTION

The present invention provides a method of masking the taste of an active ingredient which comprises incorporating the active ingredient in a microsphere-in-oil emulsion to the patient being

treated. The active ingredient can be any material which is to be orally administered to the patient but typically would be a substance which has a bitter or unpleasant taste. The present invention also provides a means for increasing the bioavailability of compounds which undergo significant hepatic "first-pass" effect. The active ingredient is incorporated into a gelled gelatin inner layer which is surrounded by an outer oil layer to form microspheres which are dispersed in an aqueous phase by homogenization. The compositions employed in the present invention often are abbreviated in the literature as s/o/w, i.e., microspheres or spheres-in-oil in water emulsions. In the present invention the s/o/w emulsion would contain a quantity of the active ingredient which is known to provide a measured amount equivalent to a unit oral dose of the active ingredient.

The present invention also provides a composition for oral administration which comprises an orally active pharmaceutically useful compound or active ingredient in a microsphere-in-oil in water emulsion.

DETAILED DESCRIPTION OF THE INVENTION

Active ingredients suitable for administering to a patient according to the present invention include any bitter of unpleasant tasting drug, e.g., gabapentin which is 1-(aminomethyl)cyclohexaneacetic acid and is a known anticonvulsant (see U.S. 4,024,175 issued May 17, 1977); tacrine which is 1,2,3,4-tetrahydro-9-acridinamine which is known to have anticholinesterase activity and to be useful in the treatment of senile dementia (see U.S. Patent Number 4,816,456 issued March 28, 1989). An example of a drug which undergoes significant hepatic

first-pass metabolic effect is [5R-(5α,7α,8ß)]-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-4-benzofuranoacetamide monohydrochloride, a kappa analgesic. Additional active ingredients which are suitable for administering to a patient in accordance with the present invention include analgesic and antiinflammatory compounds such as acetaminophen and naproxen, antihistamines, antitussives and decongestants such as diphenhydramine, pseudoephedrine, phenylpropanolamine, codeine, dextromethorphan, hydrocodone, guanifenesin, chlorpheniramine; antiepileptics such as carbamazepine, phenytoin; diuretics such as furosemide; antiasthmatics such as theophylline; hemostatics such as aminocaproic acid; antiemetics and antipsychotics such as prochlorperazine.

An active ingredient which has a high hepatic first-pass effect is one which is susceptible to being metabolized on its initial pass through the lines.

Suitable oils for forming the emulsion include edible animal and vegetable oils such as various fish oils, soybean, safflower, sunflower, corn, cottonseed, rapeseed, sesame, and bran oils, medium chain triglycerides such as Migylol 812.

An aqueous mixture of the active ingredient in gelatin is prepared by combining an aqueous solution of the active ingredient with the gelatin dissolved in a small volume of water. The gelatin is present in an amount of from 5% to 10% on a weight/volume (w/v) basis of the internal phase.

The oil phase will typically contain emulsifiers, preferably emulsifiers having a low HLB (Hydrophile-Lipophile Balance). Examples of such emulsifiers include glyceryl monostearate, glyceryl monooleate, (Crodesta F-10) sucrose distearate, sorbitan monostearate, sorbitan monopalmitate, sorbitan

monolaurate, and sorbitan esters marketed under the trade name Span.

The oil phase also typically will contain rheological agents such as Thixcin® (hydrogenated castor oil) or beeswax, to enhance the thixotropic properties of the formulation.

The gelatin mixture containing the active ingredient is heated to a temperature of about 50°C to 70°C, preferably 55°C to 65°C and mixed by stirring with the oil phase, which is at a temperature between 65°C to 75°C. The biphasic system is homogenized to obtain a sphere-in-oil (s/o) emulsion, which is then cooled rapidly to about 4°C, e.g., by placing the emulsion in an ice bath. The cooling allows for the formation of crosslinked gelatin microspheres containing the active ingredient. The s/o emulsion is then combined with water at about 15°C to 25°C and homogenized to form a microsphere-in-oil in water emulsion. The outer aqueous phase may contain emulsifiers, preferably emulsifiers having a high HLB, such as, for example, Crodesta SL 40 (sucrose cocoate), Crodesta-F-160 (sucrose stearate), ethoxylated sorbitan esters (polysorbates), sodium laurylsulfate, sodium oleate, potassium oleate, polyoxyethylenes, and ethers. It is preferred that the emulsifier used in the aqueous phase have a HLB value that is higher than the HLB value of the emulsifier used in the oil phase. The outer aqueous phase may also contain natural or artificial sweeteners such as sorbitol, sucrose, sodium saccharin, mannitol, acesulfame-K, monoammonium glycyrrhizinate, and flavoring agents and coloring agents which are generally dissolved first in ethanol. The outer aqueous phase also contains preservatives such as methyl-R propylparaben, which are also dissolved in ethanol and/or water.

The overall ratio of the three phases of the emulsion on a weight/volume basis may vary from 1% to 10% inner aqueous phase: 20% to 30% oil phase: 60% to 80% outer aqueous phase, and more preferably would be 5%:25%:70.

The concentration of the active ingredient contained in the emulsion depends on the dosage amount to be administered. The dosage amount will be the same as that which is recommended for known oral dosage forms, such as, capsules or coated tablets, of the active ingredient. The concentration of the active ingredient in the emulsion would be one which provides a recommended unit dosage amount in a specific measured volume of the emulsion.

The following example is illustrative of the formation of an emulsion of the present invention.

EXAMPLE 1

The emulsion described below contains gabapentin entrapped in crosslinked gelatin microspheres surrounded by Miglyol 812, which is emulsified to obtain the final emulsion. The sphere-in-oil emulsion is prepared with 40 volumes of oily phase and 7 to 14 volumes of aqueous phase. The internal aqueous phase has 5% w/v gelatin containing gabapentin at a concentration of 10 to 200 mg/mL.

The oily phase contains 2.1% w/v Crodesta F-10 (sucrose distearate) and 1% w/v Thixcin. After heating to about 60°C, both phases are mixed and homogenized to obtain a water-in-oil emulsion at an elevated temperature. This is followed by rapid cooling of the system to about 5°C to obtain crosslinked gelatin microspheres containing the drug. This sphere-in-oil emulsion is added to another 40 volumes of aqueous phase containing 2.1% Crodesta F-160 at 10°C to 15°C, and homogenized again to obtain

a sphere-in-oil-in-water emulsion. Sorbitol and sodium saccharin dissolved in a small quantity of water are added to the emulsion. The emulsion is then suitably flavored. The final concentration of gabapentin in this emulsion is about 20 mg/mL.

Following is the basic formula with the percentages of ingredients in the final s/o/w/ emulsion:

Ingredients	Percent in the Final Emulsion (w/v)
Gabapentin	1.0-2.0
Miglyol 812	28.6
Thixcin	0.29
Gelatin	0.5
Crodesta F-10	0.6
Methylparaben	0.18
Propylparaben	0.02
Crodesta F-160	0.6
Sorbitol	28.6
Sodium Saccharin	0.3
Cherry Flavor	0.06
Aniseed Flavor	0.03
Cinnamon	0.002
L-Menthol	0.01
Alcohol USP	5.0
Purified Water q.s. ad	100.0

EXAMPLE 2

The objective of this formulation was to evaluate the effect of the microsphere-in-oil-in-water emulsion on the oral bioavailability of drugs with high first-pass metabolism. The drug used as the example is CI-977, a new kappa analgesic which is [5R-(5α,7α,8ß)]-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4,5]dec-8-yl]-4-benzofuranacetamide monohydrochloride. The formulation is as follows:

Ingredient	Percent in Final Emulsion (w/v)
CI-977 hydrochloride	0.1
Gelatin	0.5
Safflower Oil	14.3
Soybean Oil	14.3
Thixcin-R	0.29
Crodesta F-10	0.6
Tween 80	0.5
Methylparaben	0.18
Propylparaben	0.02
Glycerin	10.0
Water for Injection q.s. ad	100.0

Procedure

A) Mix the soybean oil and the safflower oil. Dissolve the Thixcin-R and Crodesta F-10 with stirring and heat the oily phase to 65°C.

B) Dissolve the gelatin in 2.5% of water. In another container dissolve the CI-977 hydrochloride in another 2.5% of water. Mix the two aqueous solutions. Heat the solution gently to 50°C.

C) Add the aqueous solution from Step B dropwise to the oily phase from Step A with constant stirring.

D) Sonicate this primary emulsion for 90 seconds.

E) Cool this sphere-in-oil phase to about 4°C rapidly with gentle stirring.

F) In another beaker dissolve the methyl- and propylparabens in about 45% of water at 90°C. Dissolve the Tween 80 when the temperature of the water is below 50°C. Add the glycerin to this aqueous phase and cool this phase to about 25°C.

G) When the temperature of the sphere-in-oil phase is about 4°C, add the aqueous phase from Step F

with constant stirring. Pass this sphere-in-oil emulsion through a Microfluidizer once at 9000 psi.

H) Make up the volume to 100% with water for injection.

EXAMPLE 3

Ingredient	Percent in Final Emulsion (w/v)
Tacrine Hydrochloride Monohydrate	0.51*
Gelatin, Type A, 175 Bloom (Vyse Gelatin Co.)	0.5
Miglyol 812	28.6
Thixcin-R (Rheox)	0.286
Crodesta F-10	0.6
Crodesta F-160	0.6
Methylparaben NF	0.18
Propylparaben NF	0.02
Acesulfame K	0.45
Fructose USP	10.0
Glycerin USP	10.0
Sorbitol solution USP	28.6
Artificial Peppermint Flavor	0.025
L-menthol USP, Synthetic Artificial	0.025
Walnut Flavor	0.001
Artificial Vanilla Flavor	0.01
Artificial Butterscotch Flavor (A)	0.005
Artificial Butterscotch Flavor (B)	0.005
Alcohol USP	5.0
Purified Water USP q.s. ad	100.0

* Equivalent to 0.4% w/v of tacrine base.

Method of Preparation for 1000 mL of emulsion:

A) Soak the gelatin in 25 mL of cold water (15° to 30°C).

B) In another container, heat 25 mL of water to about 75°C.

C) In another container, dissolve the Thixcin R and Crodesta F-10 in Miglyol 812 with constant stirring and heating. Heat the oil phase to about 70°C.

D) Add the hot water from Step B to gelatin in Step A. Dissolve the gelatin with stirring and gently heat the solution to 60°C.

E) Add the tacrine hydrochloride to the gelatin solution from Step D and dissolve with stirring. Maintain temperature at 60°C.

F) Add the aqueous phase from Step E to the oily phase from Step C in a continuous stream and stir the mixture vigorously with a Silverson homogenizer at 5000 rpm. The aqueous phase should be added rapidly enough so that the tacrine does not remain at 60°C for more than 10 minutes.

G) Pass this primary water-in-oil emulsion through a Microfluidizer M-110F once. Collect the emulsion in an appropriate container and place the emulsion in an ice bath for rapid cooling. Stir gently with a Tekmar mixer and protect from light.

H) In another container, heat 200 mL of water to 90°C. Dissolve the methyl- and propylparabens in this hot water.

I) Remove the aqueous phase from Step H from heat and dissolve the acesulfame K and fructose in the aqueous solution. Disperse the Crodesta F-160 in the aqueous phase with constant stirring after the fructose and acesulfame K have dissolved.

J) When the temperature of aqueous phase in Step I is below 45°C, add the sorbitol solution, followed by the glycerin. Cool this phase to 25° to 30°C.

K) When the temperature of the sphere-in-oil emulsion from Step G is below 4°C, remove the emulsion from the ice bath.

L) Add the aqueous phase from Step J to the sphere-in-oil emulsion from Step K with vigorous stirring using a Silverson homogenizer at 9000 rpm. The emulsion thickens before becoming fluid.

M) Pass this sphere-in-oil-in-water from Step L through the Microfluidizer M-110F once.

N) Collect the emulsion from Step M and cool to room temperature, if necessary.

O) Dissolve the L-menthol, the two artificial butterscotch flavors, vanilla, walnut, and peppermint flavors in alcohol.

P) Add the alcoholic flavor solution to the emulsion from Step N with constant stirring by means of a Tekmar mixer at about 200 rpm.

Q) Adjust the volume of the emulsion to 1000 mL with purified water.

R) Fill the emulsion in 120 cc amber glass bottles.

S) Store the finished product in a cool place, away from light.

EXAMPLE 4

Ingredient	Percent in Final Emulsion (w/v)
Tacrine Hydrochloride Monohydrate	0.51*
Gelatin, Type A, 175 Bloom (Vyse Gelatin Co.)	0.5
Miglyol 812	28.6
Thixcin-R (Rheox)	0.286
Crodesta F-10	0.6
Crodesta F-160	0.6
Methylparaben NF	0.18
Propylparaben NF	0.02
Sodium Saccharin	0.3
Fructose USP	10.0
Glycerin USP	10.0
Sorbitol solution USP	28.6
Artificial Peppermint Flavor	0.025
L-menthol USP, Synthetic Artificial	0.025
Walnut Flavor	0.001
Artificial Vanilla Flavor	0.01
Artificial Butterscotch Flavor (A)	0.005
Artificial Butterscotch Flavor (B)	0.005
Alcohol USP	5.0
Purified Water USP q.s. ad	100.0

* Equivalent to 0.4% w/v of tacrine base.

Method of Preparation

A) In a stainless steel container, dissolve the Thixcin R and Crodesta F-10 in Miglyol 812 with constant stirring and heating. Heat the oil phase to about 70°C.

B) Soak the gelatin in a container in 25 mL of cold water (15° to 30°C).

C) In another container, heat 25 mL of water to about 75°C.

D) Add the hot water from Step C to gelatin in Step B. Dissolve the gelatin with stirring and gently heat the solution to 60°C.

E) Add the tacrine hydrochloride to the gelatin solution from Step D and dissolve with stirring. Maintain temperature at 60°C.

F) Add the aqueous phase from Step E to the oily phase from Step A in a continuous stream and stir the mixture vigorously with a Silverson homogenizer at 5000 rpm. The aqueous phase should be added rapidly enough so that the tacrine does not remain at 60°C for more than 10 minutes.

G) Pass this primary water-in-oil emulsion through a Microfluidizer M-110F once. Collect the emulsion in an appropriate container and place the emulsion in an ice bath for rapid cooling. Stir gently with a Tekmar mixer and protect from light.

H) In another container, heat 100 mL of water to 90°C. Dissolve the methyl- and propylparabens in this hot water.

I) Remove the aqueous phase from Step H from heat and dissolve the sodium saccharin and fructose in the aqueous solution. Disperse the Crodesta F-160 in the aqueous phase with constant stirring after the fructose and sodium saccharin have dissolved.

J) When the temperature of aqueous phase in Step I is below 45°C, add the sorbitol solution, followed by the glycerin. Cool this phase to 25° to 30°C.

K) When the temperature of the sphere-in-oil emulsion from Step G is about 6° ± 2°C, remove the emulsion from the ice bath.

L) Add the aqueous phase from Step J to the sphere-in-oil emulsion from Step K with vigorous stirring using a Silverson homogenizer at 9000 rpm. The emulsion thickens before becoming fluid.

M) Pass this sphere-in-oil-in-water emulsion from Step L through the Microfluidizer M-100F once.

N) Collect the emulsion from Step M and cool to room temperature if necessary.

O) Dissolve the L-menthol, the two artificial butterscotch flavors, vanilla, walnut, and peppermint flavors in alcohol.

P) Add the alcoholic flavor to the emulsion from Step N with constant stirring by means of a Tekmar mixer at about 200 rpm.

Q) Adjust the volume of the emulsion to 1000 mL with purified water.

R) Fill the emulsion in amber glass bottles.

S) Store the finished product in a cool place, away from light.

EXAMPLE 5

Ingredient	Percent in Final Emulsion (w/v)
Tacrine Hydrochloride Monohydrate	0.255*
Gelatin, Type A, 175 Bloom (Vyse Gelatin Co.)	0.5
Miglyol 812	28.6
Thixcin-R (Rheox)	0.286
Crodesta F-10	0.6
Crodesta F-160	0.6
Methylparaben NF	0.18
Propylparaben NF	0.02
Mono ammonium glycyrrhizinate	0.50
Fructose USP	10.0
Glycerin USP	10.0
Sorbitol solution USP	28.6
Peppermint Oil, highly rectified	0.04
N&A French Vanilla flavor	0.02
Bitter mask	0.10
Alcohol USP	5.0
Purified Water USP q.s. ad	100.0

* Equivalent to 0.2% w/v of tacrine base.

Method of Preparation

A) In a stainless steel container, dissolve the Thixcin R and Crodesta F-10 in Miglyol 812 with

constant stirring and heating. Heat the oil phase to about 70°C.

B) Soak the gelatin in a container in 25 mL of cold water (15° to 30°C).

C) In another container, heat 25 mL of water to about 75°C.

D) Add the hot water from Step C to gelatin in Step B. Dissolve the gelatin with stirring and gently heat the solution to 60°C.

E) Add the tacrine hydrochloride to the gelatin solution from Step D and dissolve with stirring. Maintain temperature at 60°C.

F) Add the aqueous phase from Step E to the oily phase from Step A in a continuous stream and stir the mixture vigorously with a Silverson homogenizer at 5000 rpm. The aqueous phase should be added rapidly enough so that the tacrine does not remain at 60°C for more than 10 minutes.

G) Pass this primary water-in-oil emulsion through a Microfluidizer M-110F once. Collect the emulsions in an appropriate container and place the emulsion in an ice bath for rapid cooling. Stir gently with a Tekmar mixer and protect from light.

H) In another container, take 100 mL of water at 25°C. Dissolve the fructose in this water with constant stirring.

I) Once the fructose has completely dissolved in the solution, add the sorbitol solution to the aqueous phase. Stir gently. Disperse the Crodesta F-160 in the aqueous phase with constant stirring.

J) When the Crodesta F-160 has dispersed in Step I, add the glycerin to the aqueous phase. Note that the temperature remains between 25° to 30°C.

K) When the temperature of the sphere-in-oil emulsion from Step G is about 6° ± 2°C, remove the emulsion from the ice bath.

L) Add the aqueous phase from Step J to the sphere-in-oil emulsion from Step K with vigorous stirring using a Silverson homogenizer at 9000 rpm. The emulsion thickens before becoming fluid.

M) Pass this sphere-in-oil-in-water emulsion from Step L through the Microfluidizer M-110F once.

N) Collect the emulsion from Step M and cool to room temperature, if necessary.

O) Dissolve the peppermint oil, bitter mask, and french vanilla flavors in half the amount of alcohol. Disperse the monoammonium glycyrrhizinate in this solution and add 50 mL of water to dissolve it.

P) Dissolve the methyl- and propyl-parabens in the remaining quantity of alcohol.

Q) Add the alcoholic solutions from Step Q and Step P to the emulsion from Step N with constant stirring by means of a Tekmar mixer at about 200 rpm.

R) Adjust the volume of the emulsion to 1000 mL with purified water.

S) Fill the emulsion in 30 cc amber glass bottles.

T) Store the finished product in a cool place, away from light.

The different formulations for tacrine resulted in different release patterns depending upon the type of sweetener used in the formulation. For instance, the formulation containing sodium saccharin as the sweetener results in a tacrine-saccharin complex in the outer aqueous phase of the emulsion which leads to a slower release pattern than the complex between tacrine and acesulfame-K, which is another sweetener. The use of mono ammonium glycyrrhizinate as the sweetener in the formulation did not yield a complex in situ and resulted in the fastest release of the three formulations. The dissolution medium was 0.1N

HCl in these studies. Similar trends were observed when water was used as the dissolution medium.

CLAIMS

1. A microsphere-in-oil in water emulsion comprising a system of gelled gelatin microspheres containing the active ingredient, said microspheres being surrounded by oil to form a microsphere-in-oil (s/o) emulsion and said s/o emulsion being dispersed in an aqueous phase.

2. An emulsion of Claim 1 wherein the ratio of the three phases is 1% to 10% inner aqueous phase: 20% to 30% oil phase: 60% to 80% outer aqueous phase.

3. An emulsion of Claim 2 wherein the active ingredient is gabapentin.

4. An emulsion of Claim 2 wherein the active ingredient is tacrine.

5. An emulsion of Claim 2 wherein the active ingredient is [5R-(5α,7α,8β)]-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-4-benzofuranoacetamide monohydrochloride.

6. An emulsion of Claim 1 wherein the ratio of the three phases is 5% inner aqueous phase: 25% oil phase: 70% outer aqueous phase.

7. A method of masking the taste of an active ingredient which comprises administering the active ingredient in the microsphere-in-oil in water emulsion of Claim 1.

8. A method of masking the taste of an active ingredient which comprises administering the active ingredient in the emulsion of Claim 2.

9. The method of Claim 8 wherein the active ingredient is selected from gabapentin.

10. The method of Claim 8 wherein the active ingredient is tacrine.

11. The method of Claim 8 wherein the active ingredient is [5R-(5α,7α,8ß)]-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-4-benzofuranoacetamide monohydrochloride.

12. A method of improving the oral availability of an active ingredient having high hepatic first-pass effect which comprises administering the active ingredient in the emulsion of Claim 1.

13. A method of improving the oral availability of an active ingredient having high hepatic first-pass effect which comprises administering the active ingredient in the emulsion of Claim 2.

14. The method of Claim 13 wherein the active ingredient is [5R-(5α,7α,8ß)]-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-4-benzofuranoacetamide monohydrochloride.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/01084

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 9/113

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	Chem.Pharm.Bull., vol. 30, no. 4, April 1982, T. Yoshioka et al.: "Prolonged release of bleomycin from parenteral gelatin sphere-in-oil-in-water multiple emulsion", pages 1408-1415, see the whole article (cited in the application) ---	1-6
Y	---	7-14
Y	EP,A,0322568 (HOECHST-ROUSSEL PHARMACEUTICALS INC.) 5 July 1989, see the whole document ---	7-14
Y	Chemical Abstracts, vol. 100, no. 6, February 1984, Columbus, Ohio, US; N. Garti et al.: "Multiple emulsions. Part II. Proposed technique to overcome unpleasant taste of drugs", see page 308, abstract 39543n, & J. Dispersion Sci. Technol. 1983, 4(3), 237-52 --- -/-	7-14

° Special categories of cited documents :[10]

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
24-10-1991	15. 11. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Danielle van der Haas

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	GB,A,1198513 (ROUSSEL UCLAF) 15 July 1970	

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9101084 SA 45774

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 13/11/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0322568	05-07-89	US-A- 4874605	17-10-89
		JP-A- 2111717	24-04-90
GB-A- 1198513	15-07-70	None	